Intensive intravenous infusion of insulin in diabetic cats

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Abstract: BACKGROUND Remission occurs in 10-50% of cats with diabetes mellitus (DM). It is assumed that intensive treatment improves -cell function and increases remission rates. HYPOTHESIS Initial intravenous infusion of insulin that achieves tight glycemic control decreases subsequent insulin requirements and increases remission rate in diabetic cats. ANIMALS Thirty cats with newly diagnosed DM. METHODS Prospective study. Cats were randomly assigned to one of 2 groups. Cats in group 1 (n = 15) received intravenous infusion of insulin with the goal of maintaining blood glucose concentrations at 90-180 mg/dL, for 6 days. Cats in group 2 (n = 15) received subcutaneous injections of insulin glargine (cats 4 kg: 0.5-1.0 IU, q12h; >4 kg 1.5-2.0 IU, q12h), for 6 days. Thereafter, all cats were treated with subcutaneous injections of insulin glargine and followed up for 6 months. Cats were considered in remission when euglycemia occurred for 4 weeks without the administration of insulin. Nonparametric tests were used for statistical analysis. RESULTS In groups 1 and 2, remission was achieved in 10/15 and in 7/14 cats (P = .46), and good metabolic control was achieved in 3/5 and in 1/7 cats (P = .22), respectively. Overall, good metabolic control or remission occurred in 13/15 cats of group 1 and in 8/14 cats of group 2. In group 1, the median insulin dosage given during the 6-month follow-up was significantly lower than in group 2 (group 1: 0.32 IU/kg/day, group 2: 0.51 IU/kg/day; P = .013). CONCLUSIONS AND CLINICAL IMPORTANCE Initial intravenous infusion of insulin for tight glycemic control in cats with DM decreases insulin requirements during the subsequent 6 months.

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INTENSIVE INTRAVENOUS INFUSION OF INSULIN IN CATS WITH DIABETES MELLITUS

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Short title: intensive insulin therapy in cats.

Abbreviations

DM, diabetes mellitus; CGMS, continuous glucose monitoring system; PBGM, portable blood glucose meter.

Keywords: Endocrinology, Pancreas, Feline, Hyperglycemia, Treatment.

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Conflict of Interest: Authors disclose no conflict of interest.

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Abstract

Background—Remission occurs in 10-50% of cats with diabetes mellitus. It is assumed that intensive treatment improves β-cell function and increases remission rates.

Hypothesis—Initial intravenous infusion of insulin that achieves tight glycemic control decreases subsequent insulin requirements and increases remission rate in diabetic cats.

Animals—Thirty cats with newly diagnosed diabetes mellitus.

Methods—Prospective study. Cats were randomly assigned to one of 2 groups. Cats in group 1 (n=15) received intravenous infusion of insulin with the goal of maintaining blood glucose concentrations at 90-180 mg/dL, for 6 days. Cats in group 2 (n=15) received subcutaneous injections of insulin glargine (cats ≤ 4 kg: 0.5-1.0 IU, q12h; > 4 kg 1.5-2.0 IU, q12h), for 6 days. Thereafter, all cats were treated with subcutaneous injections of insulin glargine and followed up for 6 months. Cats were considered in remission when euglycemia occurred for ≥4 weeks without the administration of insulin. Nonparametric tests were used for statistical analysis.

Results—In groups 1 and 2, remission was achieved in 10/15 and in 7/14 cats (p=0.46), and good metabolic control was achieved in 3/5 and in 1/7 cats (p=0.22), respectively. Overall, good metabolic control or remission occurred in 13/15 cats of group 1 and in 8/14 cats of group 2. In group 1, the median insulin dosage given during the 6-month follow-up was significantly lower than in group 2 (group 1: 0.32 IU/kg/day, group 2: 0.51 IU/kg/day; p=0.013).

Conclusions and clinical Importance—Initial intravenous infusion of insulin for tight glycemic control in cats with diabetes mellitus decreases insulin requirements during the subsequent 6 months.

Diabetes mellitus (DM) is a frequent endocrine disease in cats. Approximately 80% of diabetic cats are believed to have a form similar to type 2 diabetes in humans, which is characterized by inadequate insulin secretion and impaired insulin action.[1] Current cornerstones of diabetes management in cats are twice daily injections of insulin and feeding a high-protein and low-carbohydrate diet. Ten to 50% of diabetic cats experience remission and no longer require exogenous insulin because of resolution of clinical signs and normalization of blood glucose and fructosamine concentrations.[2-7]

A number of trials in human medicine evaluated short-term intensive administration of insulin in the management of newly diagnosed type 2 diabetic patients.[8-12] Treatment included either multiple daily injections or continuous subcutaneous infusion of insulin for 2 to 3 weeks. Early intensive insulin therapy resulted in improvement of β–cell function and prolongation of remission.[10] In addition, remission rates after 1 year were significantly higher in humans treated with intensive insulin therapy compared with those treated with oral hypoglycemic agents.[10-12] The effect of intensive insulin therapy in cats needs to be explored; to date, only two studies have investigated this treatment modality using the long-acting insulin analogs glargine and detemir.[13,14] Owners were required to follow a strict treatment protocol that included measurement of blood glucose several times per day. In both studies, remission rates of up to 64% and 67% were achieved, which might suggest that intensive insulin treatment is beneficial in cats.[13,14]

Because intensive insulin treatment is associated with favorable results in human patients with type 2 diabetes and appears to be advantageous in diabetic cats, the aim of this investigation was to determine the effect of early and tight glycemic control using short-term intravenous infusion of insulin in cats with newly diagnosed diabetes.

Materials and Methods

Animals

Cats with newly diagnosed diabetes were enrolled in the study from July 2008 to January 2011. Cats were excluded from the study if they had received insulin therapy for longer than 1 week before admission and if glucocorticoids or progestagens had been administered during the previous 4 months. All cats underwent a thorough evaluation including physical examination, complete blood cell count, serum biochemical profile, measurement of fructosamine and total T4 concentrations, urinalysis, including bacterial culture and urinary protein-to-creatinine ratio, blood pressure measurement, abdominal and thoracic radiographs and abdominal ultrasonography. Diabetic cats with ketoacidosis were included in the study if acidemia resolved and their general condition improved within 48 hours of insulin therapy. Cats with concurrent diseases at diagnosis (e.g., renal failure, gastrointestinal disorders, heart disease, other endocrinopathies, neoplasia) were not enrolled.

The study was approved by the Cantonal Veterinary Office of Zurich and conducted in accordance with guidelines established by the Animal Welfare Act of Switzerland (permission no.: 83/2008). Informed consent to participate in the study was provided by the owners.

Randomization and treatments

Enrolled cases were hospitalized for 7 consecutive days. The cats were allocated to one of two treatment groups using a software[a] providing a partial minimization procedure to adjust the randomization probabilities between groups and to balance for covariates collected at baseline. The covariates sex, age, body weight, treatment with insulin before admission (i.e., for <1 week), presence of ketoacidosis, blood glucose and serum fructosamine concentrations were selected.

105 After the initial work-up, all cats were sedated with midazolam/butorphanol[b,c] and
106 anesthetized with propofol[d] to place a central venous catheter[e] in the jugular vein and to insert
107 the sensor of the continuous glucose monitoring system (CGMS)[f] in the subcutaneous tissue
108 of the lateral chest wall, as described previously.[15-17] The CGMS measures glucose in the
109 subcutaneous interstitial fluid every 10 seconds and displays the 5-minute average on the
110 monitor. After a 2-hour period of initialization, the first calibration was carried out; thereafter
111 the CGMS was calibrated after 6 hours and then every 10 hours. To calibrate the CGMS,
112 capillary blood glucose was measured with a portable blood glucose meter (PBGM)[g],
113 validated for the cat.[18] In addition to CGMS measurements, capillary blood glucose
114 concentrations were also determined with the PBGM[g] every 4 to 6 hours to ensure reliability
115 of the system.
116 Cats of group 1 received intravenous infusion of insulin for 6 consecutive days with the goal
117 of achieving tight glycemic control by adjusting the insulin dosage as required. Insulin was
118 infused via the central venous catheter. The insulin solution consisted of 12.5 IU rapid-acting
119 insulin aspart[h] dissolved in 250 ml 0.9% NaCl. The solution was renewed daily, and the tube
120 was flushed with the same solution to prevent insulin adsorption to the solid surfaces of the
121 infusion sets.[19] The initial insulin dosage used in the infusion was 0.05 IU/kg/h (equal to 1
122 mL/kg/h). In addition, 0.9% NaCl infusion was given concurrently through the same catheter,
123 and the infusion rate was adjusted to maintain the total amount of intravenous fluids at 2
124 ml/kg/h. The cats were monitored 24 hours a day. The infusion rate of insulin was adjusted to
125 achieve a target glucose concentration range of 90 to 180 mg/dL. For this purpose, the
126 infusion rate of insulin was adjusted in steps of 0.025-0.05 IU/kg/h, every 15-30 minutes, if
127 necessary. The infusion of insulin was discontinued at 6:00 am on day 7 of hospitalization,
128 and at 8:00 am, the cats were started on subcutaneous injections of insulin glargine[i]. To
129 ensure that the same dosage conversion was used for each cat, an arbitrary calculation was
130 used. The total amount of insulin infused intravenously on day 6 was divided by 4. This

131 calculated dosage was administered twice daily on day 7, while the cats were still being
132 monitored by the CGMS. The cats were discharged on day 8 with insulin injections
133 prescribed twice daily. If glucose concentrations dropped below 72 mg/dL on day 7 or 8, the
134 insulin dosage was reduced by 50%.
135 Cats of group 2 were treated during the same 7-day period of hospitalization as cats of group
136 1 and received subcutaneous injections of insulin glargine;[i] tight glycemic control was not a
137 goal in this group. The insulin dosage was 0.5-1.0 IU, q12h, in cats weighing <4 kg and 1.5-
138 2.0 IU, q12h, in cats >4 kg. Additionally, all cats received an infusion of 0.9% NaCl via the
139 central venous catheter at a rate of 2 ml/kg/h. The subcutaneous dosage of insulin was not
140 adjusted during the 7-day period unless the blood glucose concentration dropped below 72
141 mg/dL, in which case the insulin dosage was reduced by 50%. The insulin dosage was
142 increased by 0.5 IU per cat, q12h, if hyperglycemia persisted after the 7 days of
143 hospitalization.
144 All cats of both groups were fed a high-protein, low-carbohydrate diet[j] during hospitalization
145 and after discharge from the clinic. The study was carried out by two internal medicine
146 residents under the supervision of two board-certified specialists in internal medicine. Cats
147 were continuously monitored during the 7 days.
148
149 *Analyses during hospitalization*
150 To calculate the duration of time that glucose was within and outside the target range in cats
151 of group 1, the glucose concentrations recorded by the CGMS and calibrated with the PBGM
152 were divided into the following ranges: hypoglycemia (<90 mg/dL), target range (90-180
153 mg/dL) and hyperglycemia (mild: 181-270 mg/dL; and moderate to severe: >270 mg/dL).
154 This calculation included all glucose values recorded with the CGMS starting 12 hours after
155 initiation of the insulin infusion (group 1) or after the first insulin injection (group 2), until
156 day 7 at 6:00 am. The percentage of glucose measurements within each glycemic range was

157 calculated for each cat in both groups. On day 8, a blood sample was collected for
158 determination of a complete blood cell count, serum biochemical profile and fructosamine
159 concentration in all cats. The central venous catheter was then removed, and bacterial culture
160 of the catheter tip was carried out.
161 Serum potassium and phosphorus concentrations were measured at admission and discharge
162 in all cats, At admission, if hypokalemia or hypophosphatemia was documented,
163 supplementation was provided with potassium chloride or phosphate diluted in the 0.9% NaCl
164 infusion and electrolytes were measured every 2 to 6 hours until the concentration
165 normalized. During hospitalization, serum potassium and phosphorus concentrations were
166 measured only if clinical signs compatible with electrolyte abnormalities were documented.
167
168 *Follow-up*
169 Re-evaluations were scheduled 1, 2-3, 6-8, 12-16 and 24 weeks after discharge from the clinic
170 and were carried out by the same internal medicine residents who cared for the cats during the
171 first week of hospitalization. The insulin dosage was adjusted based on clinical signs and the
172 results of physical examination, blood glucose curves and fructosamine levels;[1] the goal was
173 to resolve clinical signs of DM and to maintain blood glucose curves between 90 and 270
174 mg/dL and fructosamine concentrations <400 µmol/L. To exclude the development of
175 concurrent diseases, diagnostic tests including a complete blood cell count, serum
176 biochemical profile, fructosamine concentration, urinalysis, urinary protein-to-creatinine ratio
177 and blood pressure measurement were done at each re-evaluation. Abdominal
178 ultrasonography and total T4 measurement were carried out 6-8 weeks and 24 weeks after
179 hospitalization. A dexamethasone suppression test was done 6-8 weeks after discharge from
180 the clinic to rule out hyperadrenocorticism. Remission of diabetes was defined as absence of
181 signs of DM (e.g., polyuria/polydipsia, polyphagia) with normal blood glucose (72-162
182 mg/dl) and fructosamine concentrations (<340 µmol/L) for at least 4 weeks after

discontinuation of the insulin injections.[1,4,5] In cats in which remission occurred before insulin administration had been discontinued, the dosage was decreased in increments of 0.5 IU per dosage, once weekly. The last dosage before insulin was discontinued was 0.5 UI once daily, for at least one week. The onset and duration of remission were recorded. Good metabolic control was defined as absence of clinical signs of DM, fructosamine concentrations <400 µmol/L and blood glucose curve measurements ranging from 90 to 270 mg/dL.[1] In both groups, the median insulin dosage per kg per day was calculated over the 6-month study period; phases of remission were excluded from the calculation.

Statistical analysis

Data are presented as median and ranges. Differences in rate of remission and rate of good metabolic control between groups were analyzed using Fisher's exact test. Differences in laboratory results, blood pressure measurements, glucose measurements within each glycemic range during hospitalization, onset of remission and daily insulin dosage given over the 6-month study period between groups were analyzed using the Mann-Whitney U test. A commercial software[k] was used for all analyses. The level of significance was set at $p<0.05$.

Results

Animals

A total of 51 cats with newly diagnosed DM were admitted to our clinic during the study period. Thirty cats fulfilled the inclusion criteria and were enrolled in the study; each of the 2 groups consisted of 15 cats. In group 1, the median age was 11.0 years (range: 7.0-15.0) and median body weight was 5.8 kg (range: 3.4-9.0). Eleven were domestic shorthair or longhair cats, and 4 were purebred cats (Abyssinian, Burmese, Siamese and Norwegian forest cat). Nine cats were neutered males and six were spayed females. In group 2, the median age was 11.0 years (range: 8.0-17.0) and median body weight was 4.7 kg (range: 2.5-9.6). Fourteen were domestic shorthair or longhair cats and one was a Ragdoll cat. Eight cats were neutered males and seven were spayed females. There was no significant difference in gender, age or bodyweight between the two groups. At the time of initial presentation, 2 of the cats enrolled in the study had ketoacidosis, which resolved within one day of intramuscular injections of insulin; one was allocated to group 1 and the other to group 2. In group 2, 1 cat died of pyelonephritis (3 months after admission) and another died of alimentary lymphoma (3 days before the end of the study). Only cats that were alive for the duration of the study were included in the analysis; the cat that died 3 months after admission was excluded.

Laboratory results and blood pressure measurement on admission

In group 1, the median serum glucose concentration was 439 mg/dL (range: 203-581) and the median fructosamine concentration was 615 μmol/L (range: 528-783). In group 2, the median serum glucose concentration was 425 mg/dL (range: 248-560) and the median fructosamine concentration was 575 μmol/L (range: 449-778). The laboratory results and blood pressure measurements at the time of admission are shown in Table 1. There were no significant differences between groups.

225 *Intensive intravenous infusion of insulin*

226 In group 1, blood glucose concentrations decreased to the target range within 12 hours of
227 initiation of treatment in 13 of 15 cats. In those cats, it was necessary to reduce the insulin
228 infusion rate to 0.02-0.03 IU/kg/h to avoid hypoglycemia. In 2 obese cats with a body
229 condition score[1] of 9 out of 9, the initial insulin infusion rate was not sufficient to achieve the
230 target glucose concentration within 12 hours and it was therefore increased to 0.07 IU/kg/h.
231 Within 24 hours, all 15 cats had blood glucose concentrations within the target range. In 2/15
232 cats of group 1, the glucose concentration decreased below 72 mg/dL during the 6-day
233 infusion, and the insulin infusion was stopped temporarily. On day 7, 2 of the cats received
234 0.5 IU, 8 received 1 IU, 4 received 2 IU and 1 received 3 IU of insulin injected
235 subcutaneously, q12h. Bacterial culture of the tip of the jugular catheter after removal
236 revealed bacterial growth in 2 cats; one culture yielded *Pseudomonas aeruginosa* and the
237 other *Enterococcus* spp..

238

239 *Subcutaneous injections of insulin*

240 In group 2, nine of the 15 cats weighed <4 kg; the initial dosage of insulin injected
241 subcutaneously was 0.5 IU, q12h, in 1 cat and 1.0 IU, q12h, in the other 8. Of the 6 cats that
242 weighed >4 kg, 4 received an initial dosage of insulin injected subcutaneously of 1.5 IU,
243 q12h, and 2 received 2.0 IU, q12h. In 4 of the 15 cats of group 2, glucose concentrations
244 decreased to the target range within 12 hours. During hospitalization, 4 of the 15 cats of group
245 2 had glucose concentrations <72 mg/dL, which necessitated a 50% decrease in the insulin
246 dosage for the remainder of the study; the dosage was reduced after a median of 2.6 days
247 (range: 0-4). One of those 4 cats had normoglycemia at the time of discharge (day 8), and
248 insulin was therefore not prescribed. In 6 of the 15 cats the insulin dosage was increased at the
249 time of discharge because the amount given during hospitalization was considered insufficient
250 for adequate glycemic control; the insulin dosage was increased to 1 IU in one cat, to 1.5 IU

in two cats and to 2 IU in the remaining three cats, administered subcutaneously, q12h. Bacterial culture of the tip of the jugular catheter after removal revealed bacterial growth of *Pantoea agglomerans* in one cat and *Acinetobacter* spp. in one other.

Analyses during hospitalization and costs

To determine whether short-term intravenous infusion of insulin maintained blood glucose levels within the target range during hospitalization, the percentage of glucose measurements that fell into different concentration ranges was compared with those of cats that were started on subcutaneous injections of insulin without aiming at tight glycemic control. The percentage of glucose measurements for cats within the target range of 90-180 mg/dL was significantly higher for cats in group 1 than in group 2 [group 1: median 59% (range: 15-96); group 2: median 16% (range: 0-65); p=0.001]. The percentage of glucose measurements with moderate to severe hyperglycemia (>270 mg/dL) was significantly lower for cats in group 1 than in group 2 [group 1: median 5% (range: 0-40); group 2: median 42% (range: 0-100); p=0.004)]. The percentage of glucose measurements for each cat within the range of mild hyperglycemia (181-270 mg/dL) [group 1: median 27% (range: 0-45); group 2: median 20% (range: 0-83)] and of hypoglycemia (<90 mg/dL) [group 1: median 0% (range: 0-30); group 2: median 0% (range: 0-40)] did not differ significantly between groups.

In both groups, median fructosamine concentrations decreased significantly after one week of hospitalization [admission vs. discharge: group 1, 615 µmol/L (range: 528-783) vs. 402 µmol/L (range: 322-528), p<0.0001; group 2, 575 µmol/L (range: 449-778) vs. 441 µmol/L (range: 351-527), p<0.001]. Fructosamine concentrations at discharge did not differ significantly between groups.

On admission 3 cats presented with mild hypokalemia (range: 3.3-3.7 mEq/L; reference range: 3.8-5.4) and 5 with mild hyperkalemia (range: 5.5-6.5 mEq/L), 2 cats presented with mild hypophosphatemia (1.8 and 2.0 mg/dL, respectively; reference range: 2.8-5.6) and one

277 with mild hyperphosphatemia (6.2 mg/dL). Abnormal serum potassium or phosphorus
278 concentrations normalized within 24 hours from admission; potassium chloride or phosphate
279 supplementation was provided in cats with hypokalemia or hypophosphatemia, respectively.
280 None developed clinical signs suggestive of electrolyte imbalance during the period of
281 hospitalization. At discharge all cats had normal serum potassium concentrations and all but
282 one had normal phosphorus. The cat with abnormal serum phosphorus had very mild
283 hyperphosphatemia (5.8 mg/dL). There were no differences between groups at admission and
284 discharge for either electrolyte.
285 The cost of the 6-day intensive intravenous infusion of insulin was approximately US$1,700
286 per cat.
287
288 *Diabetic remission and metabolic control during follow-up*
289 The remission occurred in 10/15 in group 1 and in 7/14 in group 2, p=0.462. Of the cats that
290 went into remission, relapse occurred 4 weeks after insulin had been discontinued in one cat
291 of group 1 and 7 weeks after discontinuation of insulin in one cat of group 2. The remaining
292 cats were in remission until the end of the study. In the majority of all cats, remission
293 occurred within 16 weeks of discharge (Table 2). The onset of remission did not differ
294 between groups.
295 Good metabolic control was obtained in 3/5 cats that did not achieve remission in group 1,
296 and in 1/7 cats that did not achieve remission in group 2 (p=0.222). Overall, good metabolic
297 control or remission was achieved in 13/15 cats in group 1 and in 8/14 cats in group 2. During
298 the 6-month follow-up period, the median insulin dosage was significantly lower in group 1
299 cats compared with group 2 [group 1: 0.32 IU/kg/day (range: 0.13-0.53); group 2: 0.51
300 IU/kg/day (range: 0.05-1.52); p=0.013] (Figure 1).
301 During the 6-month follow-up period, 9 cats developed concurrent diseases, including chronic
302 kidney disease (n=4, 3 in group 1, 1 in group 2), hyperthyroidism (n=2, 1 in each group),

303 acute pancreatitis and hyperadrenocorticism (1 in group 2), pyelonephritis (1 in group 2) and

304 alimentary lymphoma (1 in group 2).

Discussion

Intravenous infusion of insulin was effective in quickly reducing glucose concentrations to within the target range, and compared with subcutaneous injections of insulin, prevented long periods of moderate to severe hyperglycemia (i.e., >270 mg/dL). Glucose concentrations were rarely below the reference range, and episodes of clinical hypoglycemia did not occur. These findings support the conclusion that our method of intensive intravenous infusion of insulin can be safely used to rapidly decrease hyperglycemia without adverse effects. In previous studies, we demonstrated that CGMS is clinically accurate for generating 12- and 24-hour glucose curves in diabetic cats.[15,16] The results of the present study showed that a CGMS is a valuable tool for long-term monitoring of glucose curves (i.e., one week) in hospitalized cats and allows fine-tuning of the insulin dosage.

Remission occurred in 10/15 cats initially treated with intensive intravenous infusion of insulin compared to 7/14 cats treated with subcutaneous injections of insulin. When cats that went into remission were excluded, good glycemic control was achieved in 3/5 cats that had been initially treated with intensive intravenous infusion of insulin and in 1/7 cats treated with subcutaneous injections of insulin. However, differences between the 2 groups were not significant, possibly because of the relatively low number of cats in the study. It was interesting to note that cats started on intensive intravenous infusion of insulin required significantly less insulin than cats started with subcutaneous injections of insulin (approximately 40% less, based on differences between median values). Roomp and Rand carried out two intensive glucose monitoring studies in cats, one with insulin glargine and the other with insulin detemir.[13,14] In both investigations, the aim was to achieve tight glycemic control by frequent monitoring of blood glucose concentration and adjustment of insulin dosage. Owners were asked to measure blood glucose concentrations of their diabetic cats at least three times daily at home and to adjust the insulin dosage with the help of a web-based protocol. The rate of remission was 64% in diabetic cats treated with insulin glargine and 67%

in diabetic cats treated with insulin detemir.[13,14] Their rates of remission were similar to our results in cats started on intensive intravenous infusion of insulin. These results suggest that strict blood glucose monitoring and frequent insulin dosage adjustments are as effective as intensive intravenous infusion of insulin. However, the study design of those previous investigations differed substantially from that of the present study making direct comparison difficult. In the study by Roomp and Rand, owners of cats with DM were responsible for maintaining tight glycemic control,[13] whereas in our study, veterinarians were in charge of insulin dosage adjustments. One would expect that treatment decisions made by veterinarians in a hospital setting are more consistent than those made by owners at home. In addition, it should be noted that in contrast to our study, a substantial percentage of the cats included in the study by Roomp and Rand had been treated with glucocorticoids before being diagnosed with DM.[13] In our study, cats with prior steroid therapy were excluded. The chance of remission in cats with glucocorticoid-induced DM is good,[13] which may explain the slightly higher remission rate found in the glargine-treated cats in their study compared with the cats of group 2, in which initial tight glycemic control was not a goal. Of note, by excluding glucocorticoid-treated cats from that study,[13] the remission rate would have decreased from 64% to 51%, yielding a remission rate similar to our group 2 cats as well as to other cats started on subcutaneous injections of insulin without initial tight glycemic control.[5]

Clinical studies in human medicine demonstrated that initial intensive infusion of insulin has positive effects on metabolic control in patients with newly diagnosed type 2 diabetes compared with oral antidiabetic drug therapy.[10-12] This beneficial effect was attributable to improved β–cell function, evidence of which was seen as augmented glucose stimulated first-phase insulin secretion after intensive infusion of insulin.[12] The mechanisms involved in improved β–cell function after intensive insulin therapy in humans include reversal of glucotoxicity and lipotoxicity and/or reduction of islet inflammation, all of which contribute to loss of β–cell function and mass.[20-22] Glucotoxicity is considered to be the major cause of

357 loss of β–cell function and mass.[22] Similar to findings in humans, hyperglycemia has been
358 shown to induce early and severe dysfunction and loss of β–cells via apoptosis in healthy
359 cats.[23-24] Thus, eliminating the detrimental effects of hyperglycemia using initial intensive
360 infusion of insulin may improve β–cell viability in diabetic cats, ultimately decreasing insulin
361 requirements for the maintenance of glycemic control. Evidence of this in the present study
362 was the lower median insulin dosages required by cats in group 1.
363 This study had some limitations including the relatively low number of cats; studying a larger
364 number of cats may or may not have shown significant differences for rates of remission or
365 good metabolic control. The follow-up period was set at 6 months and it is possible that this
366 period was too short for remission to occur in some of the cats. However, based on an earlier
367 study from our clinic, more than 90% of cats with newly diagnosed diabetes achieved
368 remission within 6 months,[5] and therefore the length of the follow-up period presumably had
369 little effect on the remission rate. The central venous catheters from 4 cats yielded positive
370 bacteriological cultures, but because none of these cats had related clinical or laboratory
371 abnormalities, it was assumed that the adverse effect of the recovered microorganisms was
372 negligible. Finally, fine-tuning of the insulin dosage to maintain blood glucose levels within
373 the target range was difficult in some cats; concentrations above the target range occurred
374 despite strict 24-hour monitoring. It is possible that in some cats this interfered with the
375 beneficial effects of intensive intravenous infusion on β–cells.
376 In summary, cats that initially received intensive intravenous infusion of insulin with tight
377 glycemic control had significantly decreased insulin requirements in the 6-month-follow-up
378 period. Remission rate and metabolic control did not differ significantly between the two
379 groups, possibly because of the small number of cases. Intensive intravenous infusion of
380 insulin is a demanding treatment, and owner compliance may not be satisfactory because of
381 the high cost and the relatively long hospitalization period.

Footnotes

[a]Minim (Altman DG, Bland JM), www.sghms.ac.uk/depts/phs/guide/randser.htm.

[b]Dormicum, Roche Pharma, Reinach, Switzerland.

[c]Morphasol, Dr. E. Gräub, Bern, Switzerland.

[d]Propofol 1% MCT, Fresenius Kabi, Stans, Switzerland.

[e]Certofix Mono Paed S, B. Braun, Melsungen, Switzerland.

[f]Guardian REAL-Time continuous glucose monitoring system, Medtronic, Munchenbuchsee, Switzerland.

[g]AlphaTRAK portable blood glucose meter, Abbott Animal Health, Maidenhead, UK.

[h]NovoRapid, Novo Nordisk Pharma, Kusnacht, Switzerland.

[i]Lantus, Sanofi Aventis, Meyrin, Switzerland.

[j]DM Purina Veterinary Diets, Medical solution, Steinhausen, Switzerland.

[k]GraphPad Prism version 4.0, GraphPad Software, La Jolla, CA, USA.

[l]Body condition chart for the cat, Nestlé Purina PetCare Research, St. Louis, MO, USA.

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456 **Tables**

457 **Table 1.** Laboratory results and blood pressure measurements in cats on initial intensive
458 intravenous infusion of insulin with tight glycemic control achieved by insulin dosage
459 adjustment (group 1) and in cats started on subcutaneous injections of insulin without the goal
460 of initial tight glycemic control (group 2).

461

		Group 1		Group 2		
Parameter	**Unit**	**Median**	**Range**	**Median**	**Range**	**Reference range**
Hematocrit	%	39	31-49	38	23-42	33-45
Leukocytes	$10^3/\mu L$	13.3	5.8-27.0	8.7	5.0-24.0	4.6-12.8
Platelets	$10^3/\mu L$	306	192-594	322	194-649	180-680
Glucose	mg/dL	439.6	203.6-582.0	425.2	248.6-560.4	72-162
Fructosamine	µmol/L	615	528-783	575	449-778	202-340
Cholesterol	mg/dL	220.1	158.3-359.1	251.0	169.9-393.8	101-263
Triglyceride	mg/dL	141.6	35.4-557.5	119.5	44.2-2247.8	26.5-115.0
Total proteins	g/dL	7.7	7.0-9.1	7.4	5.8-8.5	6.4-8.0
Albumin	g/dL	3.4	2.9-4.1	3.5	2.6-3.9	3.0-4.0
Urea	mg/dL	27.7	16.0-35.3	10.3	12.3-15.6	20.7-35.3
Creatinine	mg/dL	1.2	0.8-2.0	1.1	0.7-1.6	1.1-1.8
Sodium	mEq/L	159	151-163	160	155-166	158-165
Chloride	mEq/L	113	103-121	115	109-119	121-131
Potassium	mEq/L	4.9	3.3-5.7	4.7	3.7-6.5	3.8-5.4
Phosphorus	mg/dL	3.8	1.8-6.2	3.7	2.0-5.6	2.8-5.6
Calcium	mg/dL	10.5	9.2-12.4	9.9	7.9-11.2	9.6-11.2

Bilirubin	mg/dL	0.08	0.02-0.22	0.08	0.02-0.16	0.1-0.4
Lipase	U/L	24	14-75	26	15-75	8-26
ALP	U/L	65	37-92	61	14-111	16-43
ASAT	U/L	34	21-91	36	15-137	19-44
ALAT	U/L	92	45-326	61	32-235	34-98
Urine ketone bodies	mg/dL	0	0-40	0	0-15	0
UPC		0.41	0.02-1.64	0.24	0.03-2.82	≤0.40
Basal thyroxin	µg/dL	1.5	0.5-2.5	1.0	0.5-2.5	<3.5
Systolic blood pressure	mm Hg	129	90-162	133	110-175	<160

462 ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate

463 aminotransferase; UPC, urine protein-to-creatinine ratio.

464 **Table 2.** Onset of remission in cats started on initial intensive intravenous infusion of insulin
465 with tight glycemic control achieved by insulin dosage adjustment (group 1) and in cats
466 started on subcutaneous injections of insulin without the goal of initial tight glycemic control
467 (group 2).

Onset of remission	**Group 1 (number of cats)**	**Group 2 (number of cats)**
At discharge	0	1
≤ 4 weeks after discharge	2	3
5-6 weeks after discharge	2	0
7-16 weeks after discharge	5	2
> 16 weeks after discharge	1	1

468 **Figure captions**

469 **Figure 1.** Dot plots of median insulin dosage administered per kg body weight per day for
470 each cat during the 6-month study period in cats on initial intensive intravenous infusion of
471 insulin with tight glycemic control achieved by insulin dosage adjustment (group 1) and in
472 cats started on subcutaneous injections of insulin without the goal of initial tight glycemic
473 control (group 2). The horizontal lines mark the medians for each group.

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